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**REMARKS**

**A. Status of the Claims**

Claims 33-48, 50-56 and 58-70 are presently pending.

**B. Response to Office Action**

**1. Objection to the Specification**

The specification is objected to as containing an embedded hyperlink and/or other form of browser executable code. This objection is believed to be presently moot, in view of the above amendment to the specification. Reconsideration and withdrawal of the objection to the specification are respectfully requested.

**2. Rejection of Claims 50-54, 35 USC §112, first paragraph**

Claims 50-54 are rejected under 35 USC §112, first paragraph, because the Office Action contends that the specification, although being enabling for treating the various disorders claimed, does not provide enablement for prevention.

In this connection, the Office Action states that claims 50-54 are drawn to "methods of treating *and* preventing various conditions." However, the claims are instead drawn to "methods of treating *or* preventing various conditions." The Office Action notes that the claims are enabling for *treating* the various disorders claimed. However, the Office Action questions whether the claims are enabling for *preventing* them (cancer is specifically noted as being of concern). In view of the alternative nature of the claim language, it is respectfully submitted that the claims are enabling. In this connection, it is noted that claims can embrace some inoperative embodiments while still meeting the requirements of 35 USC §112, first paragraph.

Reconsideration and withdrawal of the rejection of claims 50-54 under 35 USC §112, first paragraph, are respectfully requested.

**3. Rejection of Claims 38 and 42 under 35 USC §112, second paragraph**

Claims 38 and 42 are rejected under 35 USC §112, second paragraph, as indefinite. It is respectfully submitted that the previously pending claim language was in compliance with the statutory requirements of USC §112, second paragraph. However,

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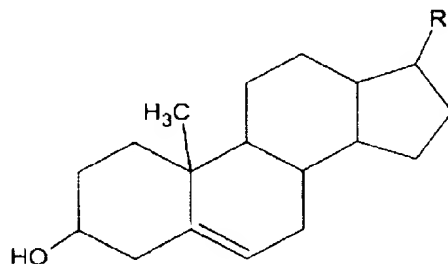
to expedite prosecution in this case, claims 38 and 42 have been amended, with no concomitant narrowing in scope. Reconsideration and withdrawal of the rejection of claims 38 and 42 under 35 USC §112, second paragraph, are therefore respectfully requested.

**4. Rejection of Claims 33-48, 50-52, 56 and 58-70 under 35 USC §103(a)**

Claims 33-48, 50-52, 56 and 58-70 are rejected under 35 USC §103(a) over U.S. Patent No. 5,770,645 ("Stamler") in view of U.S. Patent No. 5,698,738 ("Garfield"). The Applicants respectfully traverse this rejection and its supporting remarks.

In order to establish a *prima facie* case of obviousness under 35 U.S.C. §103, (1) there must be some suggestion or motivation to modify/combine the references of record, and (2) there must be a reasonable expectation of success. See MPEP §2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *Id.* The mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination or modification. MPEP 2143.01 (emphasis added) (citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)).

Claim 33, the only independent claim presently pending, is directed to a drug delivery system comprising a medical article and a nitric oxide releasing compound comprising a lipid molecule selected from (a) phosphoglycerides, (b) lipid molecules having a sphingosine base as a backbone, (c) monoacylglycerols, (d) diacylglycerols, (e) glycosylacylglycerols, and (f) sterol molecules of the formula:



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where R is a branched aliphatic chain of eight or more carbon atoms, wherein the lipid molecule further comprises a nitric-oxide containing group selected from (a) a

—S—N=O group, (b) a —O—N=O group, and (c) a  $\begin{array}{c} \diagup \\ \text{N—N=O} \\ \diagdown \end{array}$  group.

The Office Action concedes that Stamler does not teach the use of lipids in medical articles as NO-releasing molecules, but nonetheless concludes that this deficiency addressed by the teachings of Garfield. According to the Office Action one of ordinary skill in the art would be motivated to provide lipids having a nitric-oxide containing group selected from (a) a —S—N=O group, (b) a —O—N=O group, and (c) a  $\begin{array}{c} \diagup \\ \text{N—N=O} \\ \diagdown \end{array}$  group, "because lipids are known to form liposomes, wherein an additional active agent could be entrapped in the liposome which would then provide an additional therapeutic activity."

Applicant respectfully disagrees.

For example, even assuming solely for the sake of argument that one of ordinary skill in the art would have been motivated to provide an additional active agent as alleged in the Office Action, it is not seen why one of ordinary skill in the art would be motivated to provide such a additional active agent, along with an NO-donating molecule, in a liposome as a delivery vehicle in a medical article.

Moreover, even assuming solely for the sake of argument that one of ordinary skill in the art would have been motivated to use liposomes as a delivery vehicles for both an NO-donating molecule and an additional active agent in a medical article, it is not seen why one of ordinary skill in the art would use *lipid molecules* (which are relatively hydrophobic) that have nitric-oxide containing groups *as the NO-donating molecules*.

In this regard, liposomes are spherical structures consisting of a phospholipid bilayer membrane and enclosing an aqueous solution, as is well known. As a result of this structure, drugs that are incorporated into liposomes are typically water-soluble drugs, which are incorporated into the liposomes' aqueous interiors (i.e., they are encapsulated) using methods known in the art. Accordingly, it is not seen why one of ordinary skill in the art would resort to lipid molecules having nitric-oxide containing groups as NO-donating molecules as opposed to, for example, hydrophilic NO-donating polymer molecules, which can be encapsulation by the liposomes.

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Furthermore, even assuming solely for the sake of argument that one of ordinary skill in the art would have been motivated to use liposomes as a delivery vehicles for a lipid molecule comprising nitric-oxide containing groups and an additional active agent in a medical article, it is not seen why one of ordinary skill in the art would create the specific lipid molecules presently claimed, absent hindsight afforded by the present specification, rather than resorting, for example, to the known NO-donating steroids of Garfield.

For at least the above reasons, it is respectfully submitted that claim 33 is patentable over Stamler in view of Garfield under 35 U.S.C. 103(a).

At least because they are dependent upon claim 33, claims 34-48, 50-52, 56 and 58-70 are likewise patentable over Stamler in view of Garfield.

Accordingly, reconsideration and withdrawal of the rejection of claims 33-48, 50-52, 56 and 58-70 under 35 U.S.C. 103(a) as being unpatentable over Stamler in view of Garfield are respectfully requested.

#### **5. Rejection of Claims 33-48, 50-54, 56 and 58-70 under 35 USC §103(a)**

Claims 33-48, 50-54, 56 and 58-70 are rejected under 35 USC §103(a) over Stamler in view of Garfield as applied above and further in view of U.S. Patent No. 5,814,666 ("Green"). The Applicants respectfully traverse this rejection and its supporting remarks.

As noted above, independent claim 33 is presently patentable over Stamler in view of Garfield. Green, which cited as teaching the treatment of diseases using nitric oxide, does not make up for the above-noted deficiencies in Stamler and Garfield.

For example, as noted above in connection with Stamler and Garfield, even assuming *arguendo* that one of ordinary skill in the art would have been motivated to use liposomes as delivery vehicles for an NO-donating molecule and an additional active agent in a medical article, it is not seen why, absent hindsight afforded by the present patent application, one of ordinary skill in the art would use lipids (which are relatively hydrophobic) as the NO-donating molecules, as opposed to, for example, using relatively hydrophilic NO-donating molecules, which could readily be encapsulated within the liposomes.

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In this connection, please note from Example IV of Green, entitled "Method of preparation of liposomes with nitric oxide generators," that the NO generators are *dissolved in aqueous solution and encapsulated in the aqueous interior* of the liposomes.

Furthermore, as also noted above in connection with Stamler and Garfield, even assuming solely for the sake of argument that one of ordinary skill in the art would have been motivated to use liposomes as a delivery vehicles for a lipid molecule comprising nitric-oxide containing groups and an additional active agent in a medical article, it is not seen why one of ordinary skill in the art would create the specific lipid molecules presently claimed, absent hindsight afforded by the present specification, rather than resorting, for example, to the known NO-donating steroids of Garfield.

For at least these reasons, it is respectfully submitted that claim 33 is patentable over Stamler in view of Garfield and further in view of Green under 35 U.S.C. 103(a).

At least because they are dependent upon claim 33, claims 34-48, 50-54, 56 and 58-70 are likewise patentable over Stamler in view of Garfield and further in view of Green.

Accordingly, reconsideration and withdrawal of the rejection of claims 33-48, 50-54, 56 and 58-70 under 35 U.S.C. 103(a) are respectfully requested.

**6. Rejection of Claims 33-48, 50-52, 55, 56 and 58-70 under 35 USC §103(a)**

Claims 33-48, 50-52, 55, 56 and 58-70 are rejected under 35 USC §103(a) over Stamler in view of Garfield as applied above and further in view of U.S. Patent No. 5,519,020 ("Smith"). The Applicants respectfully traverse this rejection and its supporting remarks.

As noted above, independent claim 33 is presently patentable over Stamler in view of Garfield. Smith, which is cited for its teaching of wound healing using NONOate complexes, does not make up for the above-noted deficiencies in Stamler and Garfield.

For example, as noted above, it is not seen why, absent hindsight afforded by the present patent application, one of ordinary skill in the art would use lipids (which are relatively hydrophobic) as the NO-donating molecules, as opposed to, for example, using

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relatively hydrophilic NO-donating molecules, which could readily be encapsulated within the liposomes.

In this connection, see, e.g., col. 10, lines 40-42 of Smith (emphasis added): "It may be possible to use in these wound studies NONOates which are *water soluble* but are *encapsulated* in polymeric devices or *liposomes*."

Moreover, as also noted above, it is not seen why, absent hindsight afforded by the present patent application, one of ordinary skill in the art would bother to create the specific lipid molecules presently claimed, rather than resorting, for example, to the known NO-donating steroids of Garfield.

For at least the above reasons, it is respectfully submitted that claim 33 is patentable over Stamler in view of Garfield and further in view of Smith under 35 U.S.C. 103(a).

At least because they are dependent upon claim 33, claims 34-48, 50-52, 55, 56 and 58-70 are likewise patentable over Stamler in view of Garfield and further in view of Smith.

Accordingly, reconsideration and withdrawal of the rejection of claims 33-48, 50-52, 55, 56 and 58-70 under 35 U.S.C. 103(a) are respectfully requested.

### **CONCLUSION**

Applicants submit that the claims of the present invention are in condition for allowance, early notification of which is earnestly solicited. Should the Examiner be of the view that an interview would expedite consideration of this Amendment or of the application at large, request is made that the Examiner telephone the Applicant's attorney at (703) 433-0510 to resolve any outstanding issues.

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**FEES**

The Office is authorized any required fees to deposit account number 50-1047.

Respectfully submitted,



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